telephone conference on March 15, 1993, between Ms. Raz Fleshner and Examiner M. Allen concerning an IDS filed on November 13, 1989. During said telephone conference, Ms. Fleshner brought to the Examiner's attention the fact that Wetzel et al. (Gene, 16: 63-71, 1981) was disclosed in said IDS. A copy of the Form PTO-FB-A820 which was attached to the Office Action of January 21, 1992, however, failed to indicate that Wetzel et al. had been considered. All of the documents except that of Wetzel et al. were initialled.

Ms. Fleshner requested clarification as to whether the Examiner had actually considered Wetzel et al. and was told that perhaps the Examiner had indeed considered said document but had inadvertently failed to initial the citation on the PTO form. At the time of the telephone conference, the Examiner requested that Ms. Fleshner raise this issue in the next response and then the Examiner would explain what had happened. Accordingly, applicants respectfully request such an explanation.

At pages 2 and 3 of the Office Action, the Examiner objected to the specification and rejected claims 13 and 14 under 35 U.S.C. § 112, first paragraph, alleging that the specification as originally filed does not provide support for the invention as is now claimed. Applicants respectfully traverse this rejection and objection.

Specifically, at page 2, lines 24-27, the Examiner states that:

> The specification does not describe nor enable a method for producing and isolating human insulin from the intermediate for mono-Arg

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> insulin (formula I) that occurs in one vessel without having to isolate mono-Arg insulin.

The Examiner then proceeds to provide an interpretation of examples 4 and 8 and the way in which these interpretations allegedly fail to support claim 13.

Without acquiescing in the propriety of this rejection and solely to expedite prosecution, applicants have amended claim 12, upon which claim 13 depends, such that it now recites the use of "trypsin" in step (a) and further recites "cleaving the mono-Arg insulin resulting from the step (a) with carboxypeptidase B." Concerning the "one-pot reaction", it appears that the Examiner may have misinterpreted claim 13. Example 6 teaches that insulin can be produced from mono-Arg insulin by combined use of trypsin and carboxypeptidase B. Therefore, if one incubates the mono-Arg proinsulin of Example 4 with trypsin and carboxypeptidase B, one will produce mature insulin in a "one-pot reaction." Such a possibility is clearly taught in the specification, e.g., at page 5, lines 9-12, as follows:

> In comparison, mini-proinsulin can be converted to human insulin in an ideal manner in a 'one-pot reaction' simultaneously using trypsin and carboxypeptidase B or by means of enzymes have the same action.

Therefore, contrary to the Examiner's assertion, the present specification both describes and enables a method for producing and isolating human insulin from a mono-Arg insulin intermediate in one vessel without having to isolate mono-Arg insulin. If this rejection is maintained, the burden is on the Examiner to present evidence or reasons why the discussed description and enablement are doubted. Specifically for nonenablement, the Examiner must

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present evidence or reasons why one skilled in the art, in view of the specification, could not make and use the claimed invention without undue experimentation. Absent such a showing, the application is presumed enabling.

At page 3 of the Office Action, the Examiner notes "that the preamble to claim 11 upon which claim 13 formerly depended is not the same as that of claim 12 upon which claim 13 now depends." Applicants do not understand how that observation has any bearing on complying with section 112, first paragraph. If that observation is maintained as a basis for a rejection, applicants respectfully request clarification.

At page 3, the Examiner states that:

> The specification does not describe nor enable preparation of mono-Arg insulin from the intermediate for mono-Arg insulin (formula I) involving cleaving the compound of formula I with cyanogen bromide. It is noted that the specification describes use of cyanogen bromide on a fusion protein not the compound of formula I (See example 4).

It appears to the applicants that this portion of the rejection is applied to claim 14, and will address their response accordingly.

Applicants assert that it would be clear to one of skill in the art that claim 14 refers to the cleaving of compound I when the compound is in the form of a fusion protein. Without acquiescing in the propriety of the rejection, however, and solely to expedite prosecution, applicants have proposed amending claim 14 to recite "b) cleaving said expressed compound of formula I with cyanogen bromide, <u>when said compound of formula I is in the form of a fusion protein</u> ..."

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Based on the above arguments, applicants assert that the objection to the specification and rejection of claims 13 and 14 under 35 U.S.C. § 112, first paragraph, should be reconsidered and withdrawn.

At page 3, the Examiner rejected claim 1 under 35 U.S.C. § 103 as allegedly being unpatentable over either Markussen et al. (U.S. Patent No. 4,916,212) [henceforth Markussen '212] or Markussen et al. (EPO 163,529) [henceforth Markussen '529]. Applicants respectfully traverse this rejection.

Specifically, at page 3, line 24 to page 4, line 14 the Examiner states that:

> Markussen et al. ('212) specifically suggests Thr for X and Arg for Y in column 2, line 64, through column 3, line 18 for the insulin variant B(1-29)-X_n-Y-A(1-21) produced recombinantly in yeast. "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and Y is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. Rather than a vast number of species, these specific suggestions limit the number of embodiments encompassed.
>
> With respect to claim 1, applicant is claiming a product and the method of production is not stated in the claim nor is it relevant.
>
> The expectation of successfully producing the claimed compound would have been high given that both of [sic] changes from the specific embodiment produced by Markussen et al. are conservative amino acid substitution and both of these changes are to the amino acids found in human insulin.

Applicants respectfully disagree.

Applicants incorporate herein by reference, reiterate and expand upon the response dated December 2, 1992. Since Markussen '529 is applied in alternative to Markussen '212 and the Examiner has failed to distinguish between the two references, applicants'

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arguments apply equally well to both Markussen documents throughout this response. Applicants assert that the difference between the cited art and applicants' invention is considerable, given that the Thr-Arg of compound I (Specification at page 1, line 24 - Claim 1) results in advantageous processing of the compound to mono-Arg insulin. Therefore, this is not an insignificant change in the compound.

Further, applicants assert that there would have been no motivation whatsoever to substitute the amino acids of the instantly claimed invention into the applied art. Simply because the substitutions may represent conservative amino acid substitutions does not provide any motivation for actually making such a substitution. Further, there is no suggestion, whatsoever, that such substitutions would result in a more easily processed molecule. Both the motivation and a reasonable expectation of success must be present in order for the applied art to render obvious the claimed invention. Neither is present in documents cited by the Examiner.

As set forth in Markussen, '212 at column 2, lines 49-62, and in particular at column 5, lines 3-20 and Examples 14-18, Markussen refer to an insulin precursor which does not contain Thr 30 of chain B. The insulin precursor, therefore, must be converted into mature insulin by transpeptidation. The resulting insulin esters additionally need to be hydrolyzed into mature insulin. (See Examples 14-17 in Markussen '212). Applicants have informed the undersigned that such a laborious method using a precursor molecule and which in addition involves chemical

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treatment of the molecule is disadvantageous compared with the instantly claimed invention of claims 12 and 15. The instantly claimed invention according to claims 12 and 15 produces mature insulin from a proinsulin derivative directly by enzymatic cleavage without the need for transpeptidation and chemical treatment.

In a portion of the Office Action cited above, the Examiner contend that "Rather than a vast number of species, these specific suggestions limit the number of embodiments encompassed." At column 3, line 1, of Markussen '212 the disclosure states "X_n is a peptide chain with n amino acid residues", i.e., no specific amino acids are even stated. Simply because at lines 13-14, the document states that the "X may preferably be selected from the group Ala, Ser and Thr", this does not eliminate the possibility of other amino acids being substituted for "X". No reason is provided by the Examiner as to why one should choose Ala, Ser or Thr, over other possible amino acids. Therefore, unless one knows in advance, the exact composition disclosed in the instant specification, the probability of obtaining the instantly claimed invention is substantially less than in the preferred example.

Further, even the preferred combinations presented in Markussen '212 at columns 3 and 4, e.g. B(1-29)-Ser-Lys-A(1-21), B(1-29)-Ala-Ala-Lys-A(1-21), B(1-29)-Lys-Lys-A(1-21), B(1-29)-Arg-Arg-A(1-21), B(1-29)-Lys-Arg-A(1-21), B(1-29)-Arg-Lys-A(1-21) clearly fail to suggest the instantly claimed invention. As such, Markussen '212 cannot, by itself, make the instant invention obvious.

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As previously brought to the Examiner's attention in the response dated December 2, 1992 at page 5, lines 28-31:

> In fact, applicants have informed the undersigned that certain of the numerous embodiments within the scope of Markussen et al. do not work advantageously according to the presently claimed process.

This recitation considered in light of the arguments raised above concerning Markussen '212 further highlights the failure of the section 103 rejection of claim 1. Therefore, this rejection under § 103 should be reconsidered and withdrawn.

At page 4, the Examiner rejected claims 12 and 15 under 35 U.S.C. § 103 "as being unpatentable over Markussen et al. (U.S. Patent No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Balschmidt et al. (U.S. Patent No. 5,164,366)." Applicants respectfully traverse this rejection.

Specifically, at page 5, lines 1-15, the Examiner states that

> It would have been obvious to take the DNA sequence or Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys, produce the insulin precursor in yeast as taught by Markussen et al. and convert it to insulin by the method taught by Balschmidt et al. The techniques for enzymatic cleavage using trypsin for the conversion of an insulin precursor would have been well known in the art. One would have been motivated to produce this intermediate for the advantages taught by Markussen at al. and convert it to insulin for the reasons disclosed by Balschmidt et al. and Markussen et al. (See also Markussen et al. claim 29.)
>
> With respect to the methods of claims 12 and 15, it is noted that the method of production is not limited to production in one vessel or a "one-pot reaction." As such, Applicant's arguments as to the advantages of this method are moot.

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Applicants respectfully disagree and reiterate the arguments previously made in the instant response concerning the Markussen et al. documents. Applicants further contend that essential differences exist between both Markussen et al. documents and the invention of claims 12 and 15. As discussed above Markussen neither teaches nor suggests the specific changes in the molecule of the instant invention and therefore cannot teach the processes of claims 12 and 15.

There is no teaching or suggestion of obtaining insulin by the process claimed in claims 12 and 15, in either Markussen et al. document. As such, the applied art by itself fails to render the instantly claimed invention obvious.

The Examiner has newly applied Balschmidt et al. (U.S. Patent No. 5, 164, 366). The earliest possible U.S. filing date of Balschmidt et al. for the purpose of creating section 102(e) art is April 3, 1989. The instant U.S. application claims priority under U.S.C. § 119 of German Patent Application P 38 21 159.9, filed June 23, 1988. Applicants will obtain and submit a verified translation of the German priority application in order to antedate Balschmidt et al. Based on the above arguments and the antedating of the Balschmidt et al. document, applicants assert that this rejection under § 103 should be withdrawn.

At page 5, the Examiner rejected claim 14 under 35 U.S.C. § 103 as allegedly being unpatentable over Markussen et al. '212 or Markussen et al. '529 either in view of Goeddel et al. Applicants respectfully traverse this rejection.

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Specifically, at page 6, of the Office Action, the Examiner states that:

> It would have been obvious to take the DNA sequence of Markussen et al. and encode Thr at amino acid position 30 and Arg instead of Lys as taught by Markussen et al., produce the insulin precursor in *E. coli* as a fusion protein as taught by Goeddel et al., cleave away the protective peptide using cyanogen bromide as taught by Goeddel et al. and then convert it to mono-Arg insulin. The techniques for enzymatic cleavage of fusion proteins using cyanogen bromide and for the conversion of an insulin precursor to mono-Arg insulin would have been well known in the art. One would have been motivated to produce this intermediate for the advantages taught by Markussen et al.

Applicants respectfully disagree.

Applicants have already addressed the Markussen et al. documents in the previous rejections and submit that similar arguments apply to this rejection. As argued above, Markussen '212 fails to specifically suggest the changes which would result in the instantly claimed invention. Markussen '212 fails to provide either a motivation to obtain the DNA sequence according to claim 14 or a reasonable expectation of success of obtaining said sequence. As such, the combination of either of the two deficient Markussen et al. references with Goeddel et al. could not possibly result in the instantly claimed invention. Even assuming *arguendo*, that there was justification for combining Goeddel et al. with Markussen '212, one would still not obtain the instantly claimed invention. If one does not know the appropriate peptide to express (and from the cited art one can't know this), then it doesn't matter whether or not one applies the alleged teachings of Goeddel et al. to such a peptide. As argued above,

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it would have been unlikely using Markussen '212 that the appropriate peptide could be obtained as a fusion protein on which to apply the teachings of Goeddel et al. Without the appropriate peptide, one would not obtain the instantly claimed invention. As such, the Examiner has failed to make a *prima facie* case of obviousness and this rejection of claim 14 should be reconsidered and withdrawn.

At page 6, the Examiner maintained the rejection of claim 10 under 35 U.S.C. § 103 as allegedly being unpatentable over Markussen et al. '529 or Markussen et al. '212 either in view of Goeddel et al. '945. Applicants respectfully traverse this rejection.

The Examiner has maintained the rejection for reasons of record and has alleged that the "Applicant has not shown any unexpected results for the claimed fusion protein." Applicants respectfully disagree and incorporate by reference herein, and reiterate and expand upon the response filed December 2, 1992. Applicants also reiterate the previous arguments from the instant response which have been made to overcome other rejections of the claims under § 103. The Markussen et al. documents are deficient for the reasons discussed above and Goeddel et al. fails to remedy that deficiency. Based on these arguments, applicants contend that the Examiner has again failed to make a *prima facie* case of obviousness. Further, applicants maintain that unless the Examiner has made a *prima facie* case of obviousness, there is not a burden to show unexpected results for the claimed invention.

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Therefore, this rejection of claim 10 is incorrect and should be withdrawn.

At page 7, the Examiner maintained the rejection of claim 10 under 35 U.S.C. § 112, first paragraph alleging that the disclosure is enabling only for claims limited as described in the second paragraph of page 7 of the Office Action, essentially for the reasons of record. The Examiner refers to M.P.E.P. §§ 706.03(n) and 706.03(z). Applicants respectfully traverse this rejection.

Applicants incorporate by reference herein, and reiterate and expand upon the response filed December 2, 1992. Prior to addressing the specific bases for the rejection, applicants assert that neither of these sections of the M.P.E.P. are relevant to the present rejection. The second paragraph of the M.P.E.P. § 706.03(n) states in part:

> In chemical cases, a claim may be so broad as not be supported by disclosure, in which case it is rejected as unwarranted by the disclosure. If averments in a claim do not correspond to the averments or disclosure in the specification, a rejection on the ground of inaccuracy may be in order. It must be kept in mind that an original claim is part of the disclosure and might adequately set forth subject matter which is completely absent from the specification. ... Whenever an objection or rejection is made on the basis of an incomplete disclosure, the examiner should in the interest of expeditious prosecution call attention to 37 CFR 1.118.

(Emphasis added). Applicants contend that the recitation *supra* is not relevant since the Examiner has not made a rejection based on the ground of inaccuracy.

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Section 706.03(z) refers to undue breadth. The second paragraph of this section states:

> However, in applications directed to inventions and arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.

Unlike the situation referred to *supra*, applicants have provided more than a single species. At least two examples of expression plasmids (pIK10 and pSW3) are disclosed in the specification at page 13, lines 20-21. Furthermore, this section of the M.P.E.P. refers to disclosure involving claims drawn to chemicals and chemical compounds which differ radically in their properties. Applicants contend this analysis is not relevant to the instant claims, since said claims are drawn to a different fusion protein, a portion of said fusion protein including a specific peptide (i.e., mini proinsulin of the formula B(1-30)-Arg-A(1-21) with known properties and are not claims involving chemical and chemical compounds which differ "radically" in their properties.

With respect to the bases of the present rejection, the Examiner contends that there is no evidence that C-terminal fusions with insulin are operative. Applicants continue to maintain that the Examiner has provided no facts to indicate that undue experimentation would be required to make and use the claimed invention. Further, the Examiner has failed to provide any showing that a C-terminal fusion would be expected to be inoperative. In fact, the Examiner fails to even present a conclusion of "undue experimentation". Without such a showing,

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the specification is presumed enabling and applicants need not come forward with any evidence of enablement.

Applicants further assert that it is not necessary to provide an example or data showing every species of the claimed invention. Indeed, such a standard would require a prohibitively large number of examples:

> More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

In re Angstadt and Griffin, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976).

Moreover, there is no "magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.'" In re Borkowski, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Indeed, an application may be enabling even if its specification does not contain a single working example. Borkowski, 164 USPQ at 646. Therefore, in light of the proper standard for enablement that considers the need or lack of the need for undue experimentation and in light of the knowledge of those skilled in the art, applicants' specification is fully enabling and that rejection of claim 10 under 35 U.S.C. § 112, first paragraph, is incorrect and should be reconsidered and withdrawn.

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Applicants respectfully request the entry of this amendment under 37 C.F.R. § 1.116 which is believed to place the claims in better condition for allowance or appeal. Further, in view of the foregoing amendments and remarks, it is believed that the pending claims are now in condition for allowance. Applicants earnestly request issuance of a favorable action.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fees should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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By: Lawrence B. Bugaisky
Lawrence B. Bugaisky
Reg. No. 35,086

Dated: May 24, 1993

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